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## Nonallergic Asthma

### Differential Diagnosis and Treatment

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• A classification of asthma into allergic and nonallergic has gained support from the more recent studies on the underlying causes of the disease.

The majority of instances of nonallergic asthma occur after middle life and result from recurrent infections of the upper and lower respiratory tract. Status asthmaticus is a frequent complication of infectious asthma.

Chronic and intractable asthma may be present also in a patient with allergic asthma complicated by a superimposed infection of the sinuses, bronchi and lungs.

There are many secondary or precipitating causes that may bring on asthmatic paroxysms. The most important of these are acute respiratory infections, mechanical and chemical irritants, autonomic imbalance, hormonal deficiencies and psychogenic influences. These secondary causes play a more important role in nonallergic asthma because of the greater tendency to chronicity in this form of the disease.

The effective treatment of chronic asthma depends largely on the successful control of the secondary or precipitating causes of the asthmatic attacks.

The introduction of the antibiotics and corticosteroids in the treatment of infectious asthma has supplied potent weapons to combat the disease. The use of these therapeutic agents makes possible the control of two of the important pathologic lesions of asthma—bronchial infection and bronchial inflammation.

At present combined antibiotic and cortisone or hydrocortisone therapy of asthma seems to be the most rational method of preventing the disease from becoming chronic and intractable. Their value in infectious asthma is due to their anti-infective and antiinflammatory action.

When prolonged treatment is essential, combined therapy also lessens the dangers arising from the presence of masked infections.

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IN 1860, Henry Hyde Salter, an English clinician, published a classic monograph, "Asthma: Its Pathology and Treatment."<sup>14</sup> This monograph was the first to present the fundamental pathologic and clinical observations on asthma. Salter, himself a

sufferer from chronic asthma, had an excellent opportunity to study the clinical history of the disease and in particular the reflex phenomena which he believed played an important role in the attacks.

It is of historical interest that although written in the preallergic era, Salter's monograph mentions

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TABLE 1.—Salter's classification of asthma

ASTHMA	IDIOPATHIC, uncomplicated, or SPASMODIC asthma	1. EXCITING cause manifest.	INTRINSIC asthma i.e., irritant applied to the lungs themselves.	I. Asthma from fog, smoke, fumes of various kinds.
				II. Ipecacuan asthma.
	SYMPTOMATIC, complicated or ORGANIC asthma	2. No apparent exciting cause of attacks . . . . .	EXCITOMOTORY, or reflex asthma.	III. HAY ASTHMA.
				IV. ASTHMA from animal emanations.
				V. Asthma from certain airs.
				VI. Toxaemic asthma.
			CENTRAL asthma . . . . .	I. Peptic asthma.
				II. Asthma from organic nervous irritation.
				III. Asthma from peripheral cerebrospinal irritation.
				IV. EPILEPTIC, EMOTIONAL, etc.
				PERIODIC ASTHMA
		Organic cause VASCULAR.	I. Asthma complicating bronchitis, common humid asthma—senile asthma.	
		Organic cause NERVOUS . . . . .	II. Cardiac asthma.	
			Heberden's case, etc.	

instances of "hay asthma," "asthma from animal emanations," and asthmatic attacks brought on by the inhalation of ipecac powder. The latter occurred among pharmacists and medical students who inhaled the drug while dispensing prescriptions.

Salter was probably the first to use the term *intrinsic* in the classification of the causes of asthma. Since then this term has gained wide usage and the extrinsic-intrinsic grouping of asthmatic patients is now deeply rooted in the nomenclature. The designation of asthma as intrinsic has led to much confusion because it has been given different interpretations by different clinical observers. The term *intrinsic* as employed by Salter had reference to patients whose symptoms were the result of irritation of the lungs by the common inhalants and other irritants. According to Rackemann,<sup>13</sup> Alexander,<sup>1</sup> and other proponents of the extrinsic-intrinsic classification, the designation *extrinsic* covers those asthmatic patients whose symptoms are due to sensitization to inhalants, foods and drugs; whereas *intrinsic* has reference to persons with asthma that is not due to sensitivity and to those whose symptoms arise from many unrelated causes.

Swineford,<sup>15</sup> among others, has presented cogent reasons for discontinuing the extrinsic-intrinsic classification of the causes of asthma. A classification of patients into allergic and nonallergic would be less confusing and more in keeping with present-day knowledge of the underlying causes of the disease.

The concept of nonallergic asthma as a syndrome in which wheezing is the diagnostic feature is not supported by the pathologic findings. Chronic asthma is a disease characterized clinically by

wheezing respiration and dyspnea, physiologically by bronchospasm and pathologically by edema and hypersecretion of the bronchial mucous membrane. In some instances thickening of the walls of the bronchi is also present.

The extensive research which followed the von Pirquet era, a half century ago, laid the groundwork for the present knowledge of allergic phenomena and made possible a better understanding of the causes of allergic asthma. The great emphasis focused on the study of allergic asthma has, however, diverted attention from the large group of patients whose asthma comes on after middle life and in whom chronicity is a common clinical feature.

Success or failure in the management of the patients with chronic asthma of the nonallergic type depends largely on our ability to control the secondary or precipitating causes of the attacks. Before discussing the present-day procedures employed in the direct therapeutic attack on the primary causes of asthma, it is important to consider the significance of the secondary or precipitating causes.

**Climate.** Many exciting or precipitating causes of asthmatic paroxysms are recorded in the literature. Climatic influences (temperature, relative humidity, barometric pressure) have been stressed by students of the disease<sup>12</sup> since Salter's original observations. There is little doubt that asthma of the nonallergic or infectious type usually occurring past middle life is benefited by a warm, dry climate. However, in the case of a patient with allergic asthma and superimposed infection, particularly in the case of pollen-sensitive patients, the physician must first be assured that the region is

TABLE 2.—*Causes of asthma*

PRIMARY	SECONDARY (Precipitating)	PRIMARY
I. Infection (bacterial, virus) (nonimmunologic) II. Allergy plus infection (combined immunologic and nonimmunologic)	1. Acute respiratory infections 2. Climate (temperature, relative humidity, barometric pressure) 3. Physical agents (light, heat, cold) 4. Chemical irritants 5. Mechanical irritants 6. Glandular dysfunction (thyroxine, estro- gen, androgen, adrenocortical steroids) 7. Autonomic imbalance 8. Psychogenic	III. Allergy (immunologic)
CONDITIONS FREQUENTLY PRESENT IN INFECTIOUS ASTHMA		CONDITIONS FREQUENTLY PRESENT IN ALLERGIC ASTHMA
1. Suppurative sinus disease 2. Chronic bronchitis 3. Emphysema (true) 4. Bronchiectasis 5. Obstructive bronchitis 6. Bronchial stenosis 7. Chronic lung disease		1. Hyperplastic sinus disease (polyposis) 2. Allergic cough 3. Allergic bronchitis 4. Emphysema (functional) 5. Urticaria 6. Eczema 7. Gastrointestinal allergy

free of the inhalants to which the patient is sensitive. The physician who advises a change of climate assumes considerable responsibility and the patient who at great mental or financial hazard seeks relief through a change of climate and is not benefited thereby, may return with the psychic setback which results from failure. Better and more lasting improvement is usually obtained by environmental control, with attention to heating of the home, proper ventilation and the removal of irritating substances from the patient's home surroundings.

**Autonomic, Hormonal and Psychogenic Factors.** These influences play a secondary, although significant, role in initiating and prolonging attacks of nonallergic asthma. It has already been stressed that the same factors are also excitants in allergic asthmatic patients but because of the pronounced tendency to chronicity in nonallergic asthma they assume considerably more importance. The autonomic nervous system is the great regulating and coordinating mechanism of the body. As is well known, reflex stimulation of the vagus and sympathetic nerves plays a very important part in the contraction and relaxation of the smooth muscle of the bronchi. Relief of an asthmatic paroxysm by relaxation of the smooth muscle of the bronchi through epinephrine stimulation of the sympathetic terminals is one of the most effective therapeutic measures. Little is as yet known, however, of the action of other endocrine secretions—thyroxine, estrogen, androgen, pituitary and adrenal steroids—on the sympathetic-parasympathetic mechanism in its relation to asthma. Further studies on the role

of the pituitary and adrenal cortex in relation to the ketosteroid excretion may throw additional light on the asthma problem.

The revival of interest in psychosomatic medicine in recent years has placed more emphasis on the psychogenic factor in asthma. One need not stress the importance of psychodynamic influences on body function. These influences are well recognized in many chronic diseases such as those affecting the gastrointestinal, circulatory, urinary and respiratory systems. Although there is no evidence that psychic factors alone without allergy or infection can cause asthma, they may be among the most potent factors in precipitating a paroxysm or modifying the disease to the extent that the asthmatic state becomes chronic and intractable. The beneficial therapeutic effects that an adjustment to life situations has on an asthmatic patient, and the relief obtained after the correction of anxiety states, are so often observed that they cannot be overlooked. A rational viewpoint is to regard the role of the psyche in asthma somewhat between the view of those who maintain that asthma is psychogenic and the view of the skeptic who is of the opinion that psychic influences are of little or no importance.

#### DIFFERENTIAL DIAGNOSIS

A clinical diagnosis of asthma is easily made in the presence of wheezing respiration, particularly if wheezing is accompanied by dyspnea. Determination of the cause of the asthma, however, requires a more intensive search, and a thorough history is of the greatest value. History alone will frequently

**TABLE 3.—Differential diagnosis of nonallergic and allergic asthma**

HISTORY	
NONALLERGIC	ALLERGIC
1. No family history of allergy. Attacks of asthma not related to inherited predisposition.	1. Positive family history of allergy. Attacks of asthma related to inherited predisposition.
2. History of other allergic manifestations unusual.	2. History of other allergic manifestations usually elicited.
3. Occurrence of asthma more common after middle life.	3. Asthma usually occurs before middle life.
4. Attacks usually ushered in by cold or bronchitis at a time of year when bronchial infections are common.	4. Attacks come out of clear sky. Occur at a time when persons with whom patient has contact are unaffected.
5. Attacks of asthma usually single.	5. Attacks usually recurrent.
6. Each attack usually clears up without residual symptoms.	6. Mild symptoms often persist between attacks.
7. No relation of asthma to inhaled substances or foods.	7. Inhaled substances or foods are frequently found to be causes of asthma.
8. No itching of mucous membranes.	8. Itching of conjunctival, nasal and pharyngeal membranes.
9. Status asthmaticus.	9. Constitutional reactions.

**TABLE 4.—Differential diagnosis of nonallergic and allergic asthma**

EXAMINATION	
NONALLERGIC	ALLERGIC
1. Visible mucous membranes hyperemic, red.	1. Visible mucous membranes pale, glistening, edematous.
2. Mucopurulent nasal discharge and sputum.	2. Thin watery mucoid nasal discharge, mucoid sputum.
3. Smear of nasal or bronchial secretion usually shows predominance of polymorphonuclear leukocytes.	3. Smear of nasal or bronchial secretion shows predominance of eosinophils.
4. Sinus involvement, if present, is of purulent type.	4. Sinus involvement, if present, is of hyperplastic type (nasal polyps).
5. Roentgenograms of lungs usually show peribronchial thickening and in chronic asthma x-ray evidence of emphysema.	5. Roentgenograms of lungs usually show slight or no bronchial markings.
6. Skin tests usually negative.	6. Skin tests usually positive.
7. No urticaria, eczema or other allergic manifestations.	7. Urticaria, eczema, or other allergic manifestations often present.

lead to a correct diagnosis of the underlying cause or causes. When the information obtained from the history and physical examination of the patient with suspected nonallergic asthma is inadequate for diagnosis, more extensive examinations are necessary. These may include clinical laboratory studies of the sputum for bacterial flora, tests to determine whether eosinophilia is present, and routine sensitivity tests on the skin to rule out possible allergic asthma with superimposed secondary infection of the sinuses and bronchi.

A routine rhinological examination should be done to determine the appearance of the nasal and pharyngeal membranes. Pallor and swelling of the nasal and pharyngeal membranes and a translucent uvula are characteristic of uncomplicated allergic asthma. However, this classic appearance may be masked by secondary infection. In the case of asthma due to both allergy and infection, a rhinologic examination will disclose the existence of suppurative or hyperplastic sinus disease. The recurrent polyposis in the latter condition may lead to narrowing of the bronchi through the nasal-pulmonary reflex, a mechanism which needs further study.<sup>4</sup>

Roentgenograms of the lungs in infectious asthma usually show peribronchial thickening and, in per-

sons with chronic asthma, evidence of emphysema. Visualization of the bronchial tree, which can be done with a little more discomfort to the patient and only slightly more expense, will yield vastly more information. Bronchograms may show the presence of bronchiectasis and narrowing of the bronchi and mediastinal and peribronchial masses from other causes—foreign bodies, polyps and kinks from contracting scars.

Because of the chronicity of nonallergic asthma, the question of a cardiac component must be considered. Although chronic asthma and heart disease may occur together, so-called cardiac asthma usually occurs in patients with a known history of heart disease which has imposed a load on the left ventricle. If the bronchi respond to the pulmonary congestion by spasm or if the lumina of the bronchi are narrowed by edema of the bronchial mucosa, asthmatic wheezing rales may be present. In that event, asthma of long standing may be associated with chronic emphysema and enlargement of the right side of the heart, resulting in cor pulmonale. One should, therefore, rule out the cardiac factor by clinical observation, physical examination, electrocardiogram and x-ray studies.

TABLE 5.—*Diagnostic procedure in nonallergic asthma*

1. History
2. Physical examination
3. Skin tests
4. Rhinoscopic
5. Roentgenograms of lungs
6. Bronchogram
7. Bronchoscopy
8. Electrocardiogram
9. Laboratory
  - Sputum—Routine culture
  - Sensitivity tests for antibiotics
  - Nasal smear
  - Blood count (eosinophilia)
10. Pulmonary function
  - Timed vital capacity
  - Maximum breathing capacity

### TREATMENT

There are few chronic illnesses which present such a therapeutic challenge to the physician as does chronic asthma. Effective treatment, particularly of patients in status asthmaticus has been greatly aided by the advances in knowledge of antibiotics and adrenocortical steroids. These, however, should not lessen the interest in general and preventive measures. Patients with chronic asthma of the infectious type require careful supervision. Proper nutrition is essential and except in instances of allergic asthma complicated by secondary respiratory tract infection in which sensitization to foods is unmistakably present, rigid restrictions in diet may be harmful to an already debilitated patient. Vitamin supplements and the correction of any existing anemia are important. Instructions to patients with chronic asthma should include instruction as to dietary habits and environmental control, the early treatment of acute respiratory infections, and avoidance of fatigue, emotional stress and undue physical effort.

Drugs play an important role in the treatment of asthma. The value of epinephrine, ephedrine, aminophyllin and antihistamines is too well known to require more than mention. It is unfortunate that their introduction in the treatment of asthma has lessened interest in the iodides. The iodides are particularly helpful in the treatment of chronic infectious asthma where the tenacious sputum is an important problem. Iodides may lessen the tendency to exhausting cough, so prevalent in infectious asthma, by keeping the sputum more fluid. In Hyde Salter's day, the iodides were hailed as the most important drugs in the treatment of chronic asthma and Salter devoted many pages of his monograph to stress their value.

**Antibiotics.** The introduction of antibiotic therapy in the control of respiratory tract infections and

of infectious asthma has made possible a fundamental attack on the causative bacteria. Prolonged or long-term treatment with antibiotics is more effective not only in preventing early relapses, but also in controlling chronic infectious asthma. In these instances, choosing the appropriate antibiotic and the method of administration is very important.<sup>6</sup>

Cultures and sensitivity tests should be made promptly. Material for sensitivity tests may be obtained from the infected sinuses, which are among the commonest causes of acute infectious asthma, or from a specimen of deep sputum. Where bronchoscopy is indicated, as in the event of complicating bronchiectasis, mucous plugs removed in the process may be cultured and tested. Until the results of sensitivity tests are known, the selection of an antibiotic is of necessity empirical. In these circumstances a broad spectrum antibiotic may be used.

Of utmost importance is the immediate and effective control of acute upper and lower respiratory tract infections in the early stages. If the results of sensitivity tests are not available, the oral administration of broad spectrum antibiotics which attack both Gram-positive and Gram-negative organisms will frequently give better results. Oral antibiotic therapy should be continued for at least five or ten days until the secretions from the sinuses and the sputum have become less purulent. This will prevent the transition from an acute to a chronic respiratory infection resulting in infectious asthma. Inadequate dosage may give temporary relief but will not spare the patient the discomfort of asthma lasting weeks or months. Early, adequate antibiotic therapy, therefore, becomes one of the most valuable measures in preventing an acute infection of the sinuses, bronchi or lungs from bringing on recurrent asthmatic paroxysms.

In the control of chronic infectious asthma, prolonged antibiotic therapy may be carried out over a period of months or several years. When so used, the antibiotic must be carefully selected. Sensitivity tests must be the guide, even though not infallible, because of the changing bacterial flora which may follow antibiotic therapy.

In status asthmaticus, where time is of the essence, an injectable antibiotic should be used. Penicillin is the one most widely given despite the well known anaphylactic reactions. This hazard may be lessened by combining penicillin in the same syringe with an injectable antihistaminic drug.

Aerosols have been highly recommended as an effective method for long-term treatment of chronic infectious asthma. This method of antibiotic therapy has some advantages. It is comparatively safe, free from side reactions, except for oral and pharyngeal irritation, and permits of self-administration by

simple and economical techniques. It is questionable, however, whether the blood levels of the antibiotics obtained by aerosolization are sufficient to be of value except in the less severe forms of infectious asthma.

**Steroid Hormones.** The profound effect produced by the corticosteroids on metabolism and especially on the balance of the electrolytes has been the subject of intensive research ever since their importance in therapy became known. The role of these hormones in infections is thus far little understood. It has been suggested that they lessen the inflammatory reaction and thereby the tendency to localization of the infection. Their anti-infective action may be due not to their inhibition of bacterial growth, but rather to the protection which they give the cells of the host against the liberated bacterial toxins.<sup>9</sup> Regardless of the lack of a satisfactory explanation of the mode of action, the value of the steroid hormones in infectious asthma is now well established.<sup>3, 8</sup> When properly used they are one of the most important additions to the therapy of status asthmaticus.

Where prolonged treatment with cortisone or hydrocortisone is used, the well known safeguards against untoward reactions must always be carried out. The proper selection of patients and the maintenance of dosage at the lowest level necessary to keep the patient symptom-free are essential for the safe employment of these hormones. Atrophy of the adrenal cortex may follow long-term therapy with these steroids. This can be in part overcome by the simultaneous injection of ACTH gel during the period of prolonged oral or intramuscular use of the hormones.

When the asthmatic attacks become resistant to all the well known methods of treatment and result in status asthmaticus, hydrocortisone or corticotropin may be given by slow intravenous infusion. This method of therapy has the advantage of bringing the hormones in quick contact with the tissues and cells of the host. Intravenous infusion in critically ill patients with status asthmaticus should be accompanied by intramuscular injections of cortisone or hydrocortisone until the emergency has been met. The presence of other infections is no contraindication to the unrestricted use of these steroids in chronic intractable asthma, particularly when combined with antibiotics. The latter will lessen the hazard of other masked infections which may be present. Combined treatment with adrenocortical hormones and antibiotics has been shown to be more effective than therapy with either steroids or antibacterial drugs alone.<sup>7</sup>

**Physiotherapy.** The importance of physical methods of improving respiration was stressed by

TABLE 6.—Treatment of nonallergic asthma

1. GENERAL AND PREVENTIVE MANAGEMENT
  - Rest
  - Diet
  - Nutrition
  - Correction of anemia and hormonal dysfunction (thyroid, estrogen, androgen)
  - Removal of focal infection (teeth, paranasal sinuses)
  - Early effective treatment of acute respiratory tract infections
2. ENVIRONMENTAL CONTROL AND DESENSITIZATION IN COMBINED FORMS (allergy plus infection)
3. DRUGS
  - Iodides
  - Adrenalin
  - Ephedrine
  - Aminophyllin
  - Antihistamines
4. ANTIBIOTICS
5. ADRENOCORTICAL STEROIDS AND CORTICOTROPIN
6. COMBINED ANTIBIOTIC AND ADRENOCORTICAL STEROID THERAPY
7. PHYSIOTHERAPY (breathing exercises)
8. PSYCHOTHERAPY

the Asthma Research Council of London more than 20 years ago.<sup>10</sup> It is well known that in normal breathing the respiratory muscles alter the configuration of the thorax so that on inspiration air inflates the lungs. This air is expelled by the elastic recoil of the lungs with each expiration. During an asthmatic paroxysm, inspiration becomes easier than expiration. The accessory muscles of respiration are able to overcome the obstruction caused by the generalized spasm of the smooth muscle of the bronchioles and the edema of the mucous membranes of the bronchi. Because of this obstruction in the bronchi, frequently aggravated by the development of mucous plugs, the lungs become over-distended. The degree of emphysema which develops and its reversibility or irreversibility depends largely on the chronicity of the asthmatic condition. In the less severe and less chronic forms of asthma, an asthmatic paroxysm causes only temporary over-distention of the lungs, which return to normal after the attack.

The resulting emphysema is not associated with irreversible changes in the thorax and lungs and may be designated as functional emphysema. If such attacks are of long duration and occur over a period of years, the chest adapts itself to the over-distended lungs and assumes a barrel shape with widening of the costal angles and a secondary enlargement of the lungs. True emphysema of this type is not an unusual finding in chronic asthma.

The primary object of breathing exercises in asthma is to restore the lungs and chest cavity to normal size. Such exercises will often improve the excursion of the lower ribs and diaphragm and restore the lungs and thorax to a comparatively

normal state. Exercises designed to encourage diaphragmatic breathing are useful in functional emphysema associated with the less intractable forms of chronic infectious asthma. Abbreviated abdominal breathing has been suggested also as a prophylactic measure in bringing a beginning asthmatic paroxysm under control.<sup>2,5</sup> Thus far, the method of evaluating improvement in pulmonary ventilation which may result from breathing exercises has been limited to hemithorax measurements. A more exact method of measuring the degree of bronchial obstruction as it affects the ventilation capacity in a chronic asthmatic patient both at rest and following exercise will no doubt be developed. The intensive studies on pulmonary function<sup>16</sup> now being carried out in many hospital laboratories in the United States should yield very valuable information on the effectiveness of physical exercises in chronic asthma.

**Psychotherapy.** The psychotherapeutic management of a patient with chronic intractable asthma differs only in minor details from that employed in the psychotherapy of any chronic disease. In an asthmatic child, whether the condition be due to allergic causes or is an aftermath of infectious disease—bronchitis, pneumonia, whooping cough or measles—the emotional pattern may be shaped to a great extent by family environment. In recent years greater emphasis has been placed upon maternal influences. This, however, is not true of patients past middle life in whom chronic intractable asthma develops as a result of infection. In this older group of patients, the pattern of behavior usually has been well established before the onset of the distressing symptoms which characterize recurrent asthmatic paroxysms. An anxious, depressed, dependent and phobic person will naturally have a more violent emotional response to such attacks than one who, when in good health, has shown emotional stability and normal adjustments to life situations.

Every understanding physician uses psychotherapy in the care of patients. Much of what he may do is inherent in the doctor-patient relationship. To be successful in the management of the emotional problems of patients with chronic asthma, the physician must take the time to advise, suggest and reassure.

In the majority of instances the physician who treats the organic causes underlying a patient's asthmatic condition is in the best position to minister to the patient's psychotherapeutic needs. However, where the situation demands the more specialized techniques, he should refer the patient to a cooperative psychiatrist. The psychiatrist is qualified by training to know the significance of the

psychologic stresses which may give rise to such emotional responses as anxiety, fear, resentment, hostility, frustration, rivalry and guilt. The fruitful results achieved by the cooperation of a rhinologist when the asthma problem is complicated by sinus disease should encourage similar cooperation on the part of the psychiatrist when the correction of a fundamental psychogenic component is essential for a successful result.

Centuries ago Socrates<sup>11</sup> with his profound insight must have had in mind the psychosomatic approach to the treatment of disease when he admonished: "Let no one persuade you to cure him until he has given you his soul to be cured, for this is the great error of our day in the treatment of the human body, that physicians separate the soul from the body."

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